4-Methylethcathinone (4-MEC)

Critical Review Report

Agenda Item 4.3

Expert Committee on Drug Dependence

Thirty-eighth Meeting

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World Health Organization

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Summary

4-Methylethcathinone (2-(ethylamino)-1-(4-methylphenyl)propan-1-one), also known as 4-MEC, has emerged in recent years as a recreational psychostimulant. Its homolog mephedrone (4-methylmethcathinone) is listed as a Schedule II substance under the 1971 United Nations Convention on Psychotropic Substances. The first official notification submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by a European member state was 2010. Since then it has been detected across the globe and marketed as a "research chemical" although it has also been detected as a constituent in branded products available for purchase *via* the Internet or brick-and-mortar shops.

At the 36th meeting of the WHO Expert Committee on Drug Dependence in June 2014, the Committee discussed a critical review report on 4-MEC and recommended that 4-MEC not be placed under international control at that time due to insufficiency of data regarding dependence, abuse and risks to public health but be kept under surveillance.

The majority of literature published since the 36th ECCD meeting deals with methods of chemical analysis but additional data are available from *in vitro* and *in vivo* studies. 4-MEC is a psychostimulant with monoamine transporter activity with indications of abuse liability. Some data obtained from the analysis of user reports suggest that 4-MEC produces euphoria, a sense of well being, psychostimulant effects and lack of comedown symptomatology and that these appear to be less intense and short-lived compared to mephedrone. Conflicting information is available related to the urge of redosing, craving and bingeing. Negative effects associated with 4-MEC use include excessive sweating in the armpits, nausea, and vomiting but also jaw clenching, nystagmus, heart palpitations, loss of sight and migraine.

The available data so far also suggest that it may also function as a serotonin releasing agent but not dopamine, which would differentiate it from its homolog mephedrone. Further studies are needed to assess the dependence potential. The number of case reports that demonstrate a causal relationship between 4-MEC consumption and fatal intoxication is relatively limited. There is no known therapeutic and medical use.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

1225617-18-4 (free base)
1266688-86-1 (hydrochloride salt)
1359736-80-3 (hydrobromide salt)
1346747-06-5 (N-C_2D_5 free base)
1346602-57-0 (N-C_2D_5 hydrochloride salt)
1388142-29-7 (*R*-enantiomer free base)
1388142-30-0 (*S*-enantiomer free base)

C. Other Chemical Names

4-MEC, 4-methylethcathinone, (±)-4'-methyl-*N*-ethylcathinone, 4-methyl-*N*-ethcathinone, *p*-methyl-*N*-ethcathinone, 2-(ethylamino)-1-(*p*-tolyl)propan-1-one, *p*-methylethcathinone.

D. Trade Names

Not applicable

E. Street Names

4-MEC

F. Physical Appearance

4-MEC HCl is a white crystalline powder.

G. WHO Review History

A critical review report on 4-MEC was discussed in June 2014 at the 36th meeting of the WHO Expert Committee on Drug Dependence.[1] The Committee recommended that 4-MEC not be placed under international control at that time due to insufficiency of data regarding dependence, abuse and risks to public health but be kept under surveillance.[2] The majority of literature published since the 36th ECCD meeting deals with methods of chemical analysis but additional data are available from *in vitro* and *in vivo* studies. 4-MEC is a psychostimulant with monoamine transporter activity with indications of abuse liability. The available data so far also suggest that it may also function as a serotonin releasing agent but not dopamine, which would differentiate it from its homolog mephedrone.

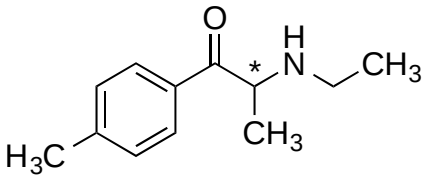
2. Chemistry

A. Chemical Name

IUPAC Name: 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one
CA Index Name: 2-(Ethylamino)-1-(4-methylphenyl)-1-propanone

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral center

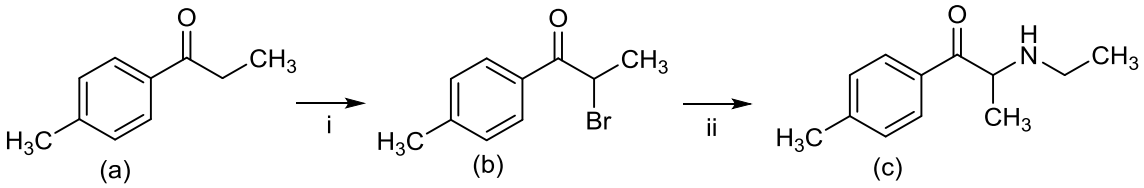
Molecular Formula: $C_{12}H_{17}NO$
Molecular Weight: 191.27 g/mol

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-4-MEC and (*R*)-4-MEC, respectively. Available information suggests that the racemic form of 4-MEC is available on the market.

D. *Methods and Ease of Illicit Manufacturing*

Information about illicit manufacturing is unavailable. One approach to 4-MEC synthesis[3] is based on a well-established standard procedure that includes the α-bromination (step i) of the propan-1-one precursor (a) and formation of the 2-bromoppropan-1-one intermediate (b). Reaction with *N*-ethylamine (step ii) gives 4-MEC (c), which may then be converted into a range of salts. Illicit manufacturing of this substance is expected to be simple and straightforward.



E. Chemical Properties

Melting point (hydrochloride salt): 191 °C (dec.),[4] 210.4 °C,[5] 205 ± 3 °C.[6]
Hydrobromide salt: 206.08 °C (acetone).[7, 8]
Boiling point: Not reported.
Solubility (hydrochloride salt): ~10 mg/mL in phosphate-buffered saline (pH 7.2); ~12.5 mg/mL in DMF; ~30 mg/mL EtOH and DMSO.[9]

F. Identification and Analysis

A range of routine and standard methods can be applied for the chemical analysis of 4-MEC in tablet, powder or liquid form. More sensitive analytical techniques may be needed (e.g. single or multistage mass spectrometry detection) for the detection of this substance in biological matrices with low concentration. Table 1 (Annex 2) provides a list of representative examples published in the scientific literature since the 36th meeting of the WHO Expert Committee on Drug Dependence.[1]

3. Ease of Convertibility Into Controlled Substances

No information available.

4. General Pharmacology

Similar to other well-researched psychostimulants, a key principle involved in the molecular mechanisms of 4-MEC is the interaction with transport proteins that lead to the elevation of extracellular neurotransmitter levels, most notably, dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively. The key targets of interest normally include the evaluation of drug action at the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters. An important question relates to the ability of a psychostimulant to act as a monoamine re-uptake inhibitor (e.g. cocaine-like) or as a substrate-type releaser (amphetamine-like). In the latter case, this may be achieved by transporter-mediated translocation of the drug into the cytoplasm in exchange of the monoamine and increase of cytoplasmic levels by affecting storage in vesicles, thus leading to increasing monoamine availability for further release.[10]

A. Routes of administration and dosage

4-MEC is frequently taken by insufflation and oral administration (dissolved in liquids, encapsulated in capsules, or wrapped in paper). Other, less-favored routes that have been described by recreational users included "eyeballing," rectal, and intravenous administration.[11] However, 4-MEC, similar to some other ring-substituted synthetic cathinones, has also been reported to be injected by users who frequently inject other drugs (Section 14).

Oral dosage levels have been tentatively suggested to range between 15-50 mg (threshold) and 150-300+ mg (strong) whereas threshold levels obtained from nasal insufflation were suggested to range between 5-25 mg (strong: 100-200 mg). The total duration of intoxication may last between 2-5 hours (p.o.) or 2-3 hours *via* nasal insufflation.[12, 13]

B. Pharmacokinetics

Data from forensic toxicology casework suggest that 4-MEC is still detectable as the parent drug in biological matrices (blood and urine) (Table 4, Section 5). Data on detection windows of 4-MEC are not available but information about the identity of metabolites has been obtained from *in vitro* studies with human liver microsomes,[14, 15] and from analyses of biological specimen.[15-17]

Overall, the key steps involved include reduction of the keto group, *N*-deethylation, hydroxylation of the 4-methyl group followed by further oxidation to the corresponding 4-carboxy metabolite, and combinations of these steps. In one study, glucuronidation could only be observed for the hydroxy-tolyl metabolite.[15] 4-MEC, dihydro-4-MEC, *N*-deethyl-4-MEC and *N*-deethyl-dihydro-4-MEC were identified in human urine[17] although dihydro-4-MEC might also be formed during storage in blood and plasma.[16] 4-MEC, dihydro-4-MEC, *N*-deethyl-4-MEC, *N*-deethyl-dihydro-4-MEC and hydroxytolyl-4-MEC have also been identified in forensic casework samples.[16] Development of an analytical LC-MS^n screening method and application to authentic urine samples revealed the detection of 4-MEC, *N*-deethyl-4-MEC, two *N*-deethyl-dihydro-4-MEC isomers, dihydro-4-MEC, 4-carboxy-4-MEC and 4-carboxy-dihydro-4-MEC, respectively.[15]

C. Pharmacodynamics

Information about the *in vitro* properties of 4-MEC is summarized in Table 2. Available data suggest that 4-MEC primarily functions *via* its interaction with monoamine transporters, which is consistent with the profiles shown by other psychostimulants. However, important differences in their mode of action have come to light which might be relevant for the fact that 4-MEC has so far shown to be less potent than, for example, mephedrone in a variety of *in vitro* and *in vivo* assays (Table 3).

In vitro pharmacology

Whereas mephedrone has been shown to act as a non-selective substrate for DAT, NET and SERT,[18-20] 4-MEC has been revealed to show a 'hybrid' character,[21] i.e. acting as a SERT substrate but as a DAT blocker in rat brain synaptosomes.[22] Uptake inhibition at hNET[23-25] and substrate-type behavior at NET have also been mentioned.[25]. Evaluation of the existing pharmacodynamic data (Table 2) indicates that 4-MEC is less potent than mephedrone in a variety of assays, possibly reflecting the induction of serotonin release compared to catecholamine reuptake inhibition. Additional multi-target screens revealed some moderate to low affinity to a number of receptors with K_i values below 5.5 µM, such as 5-HT_{2A} (3.8 µM), 5-HT_{2C} (5.2 µM) [24] and $Sigma_2$ (K_i = 1.718 µM).[23]

Table 2. 4-MEC *in-vitro* uptake and release data [a]

Uptake inhibition			**Release**			**Affinity**			**Ref**
DAT IC_{50}/nM	NET IC_{50}/nM	SERT IC_{50}/nM	DAT EC_{50}/ nM (E_{max} %)	NET EC_{50}/nM (E_{max} %)	SERT EC_{50}/nM (E_{max} %)	DAT K_i/nM	NET K_i/nM	SERT K_i/nM	
565	1,668	1,798	--	--	--	>10,000	>10,000	41	Iversen *et al.*[23]
4,280	2,230	7,930	Inactive	Inactive	Yes [b]	890	6,800	7,700	Simmler *et al.*[24]
~800 nM [c] ~3900 nM [d]	-- --	~500 nM [c] ~10,900 nM [d]	Inactive	Inactive	~100 nM [c]	--	--	--	Saha *et al.*[22]
960	930	218	>100,000	710	1,520	3,000	15,800	12,600	Boos[25]
Additional 4-MEC *in vitro* data									
Binding affinity towards other receptors with K_i value below 10,000 nM: $Sigma_2$ receptor (K_i = 1718 nM) following the NIMH-PDSP screening protocol.[26]									Iversen *et al.*[23]
Binding affinity towards other receptors with K_i value below 5,500 nM: 5-HT_{2A} (K_i = 3800 nM) and 5-HT_{2C} (K_i = 5200 nM).									Simmler *et al.*[24]
4-MEC evoked inward current in *Xenopus* oocytes expressing SERT. Greatest magnitude of current observed at 30 μM 4-MEC equivalent to 10 μM 5-HT.									Saha *et al.*[22]
Binding affinity towards rat and mouse trace amine-associated receptor 1 > 20 μM; also reported in ref[24].									Simmler *et al.*[27]
Cell viability test using the MTT assay on isolated rat hepatocytes. EC_{50} for 4-MEC = 1.29 mM and other substances for comparison included 3,4-methylenedioxymethamphetamine (MDMA) (EC_{50} = 0.754 mM), methylone (EC_{50} = 1.18 mM) and 3,4-methylenedioxypyrovalerone (MDPV) (EC_{50} = 0.742 mM), respectively. Drugs were exposed to cells for 48 h at 37 °C.									Araújo *et al.*[28]
Evaluation of potential cytotoxic effects using primary rat hepatocytes (PRH) and HepaRG cells. MTT assay: hepatocytes and HepaRG cells were exposed to test drugs for 24 h. 4-MEC: EC_{50} = 0.835 mM (PRH) and 3.905 mM (HepaRG) and comparison included MDMA: EC_{50} = 1.070 mM (PRH) and 3.854 mM (HepaRG), methylone: EC_{50} = 1.262 mM (PRH) and 5.623 mM (HepaRG), MDPV: EC_{50} = 1.070 mM (PRH) and 3.854 mM (HepaRG), respectively. All remaining tests performed in primary rat hepatocytes. Lactate dehydrogenase (LDH) assay: 4-MEC exposure (24 h) induced concentration-dependent LDH leakage (0.2-1.6 mM). At 1.6 mM 4-MEC was significantly less effective than MDMA ($p<0.05$). 4-MEC displayed concentration-dependent reducing power (Fe^{3+} to Fe^{2+}) but MDMA did not under the conditions used; MDPV induced a comparatively weak reducing potential.									Valente *et al.*[29]

Formation of intracellular reactive oxygen (ROS) and nitrogen (RNS) species were observed following 4-MEC exposure (24 h) at 0.4-1.6 mM levels. The 0.4 mM and 1.6 mM levels induced higher ROS and RNS levels than MDMA ($p<0.05$). Intracellular levels of glutathione (GSH) and glutathione disulfide (GSSG, oxidized form) evaluated using the DTNB- GSSG reductase recycling assay. Reduction of GSH (1.6 mM 4-MEC, 24 h) and increase of GSSG 1.6 mM 4-MEC, 24 h) were observed. 4-MEC did not induce a significant change in intracellular ATP levels (bioluminescence assay) compared to control. Compared to control, caspase 3, 8, and 9 activities were increased significantly following exposure of 4-MEC (1.6 mM, 24 h). No significant changes observed at 0.2-0.8 mM levels. Hoechst 33342/propidium iodide fluorescent staining to assess morphological changes in hepatocytes undergoing apoptosis or necrosis. Fluorescence microscopy revealed that 4-MEC application (0.8 mM and 1.6 mM) resulted in formation of early and late apoptotic cells and necrotic cells (1.6 mM only).	

[a] Ref[23]: National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH-PDSP).[26]

[b] Ref [24]: Qualitative assessment. 5-HT release, but not DA and NE, was considered statistically significant relative to pseudo efflux. Test drug was incubated at one concentration of 100 μM test drug. Transporters were expressed in HEX 293 cells.

[c] Ref[22]: Obtained from rat brain synaptosomes.

[d] Ref[22]: Obtained from hDAT and hSERT expressed in HEK 293 cells.

In vivo pharmacology

Information about the *in vivo* properties of 4-MEC is summarized in Table 3. The available data suggest that 4-MEC induced psychostimulant-type behavior somewhat comparable to methcathinone, amphetamine and cocaine. However, 4-MEC appeared to be much less potent, thus, requiring higher dosage levels.

Table 3. *In vivo* assay data for 4-MEC

Behaviour	**Neurochemistry / physiological responses / etc.**	**Ref**
Locomotor activity: [a] 4-MEC produced time- and dose-dependent stimulation of locomotor activity in doses from 30 to 100 mg/kg (ED_{50} = 21.09 mg/kg). Comparison with methcathinone: ED_{50} = 1.39 mg/kg). 4-MEC stimulant effects occurred within 30 min following injection and lasted 110 min. During the period of peak effect (30–60 min), locomotor activity increased to a peak of 190% of vehicle control following 10 mg/kg. In contrast to other test drugs, [a] 4-MEC did not show an inverted U-shape dose-response. Stimulant effects had a slower onset than for the other compounds (30-60 min vs. 0-30 min). Drug discrimination: [b] 4-MEC fully substituted for the discriminative stimulus effects of methamphetamine and cocaine. ED_{50} = 8.69 mg/kg (methamphetamine trained rats), ED_{50} = 12.54 mg/kg (cocaine trained rats). Comparison with methcathinone: ED_{50} = 0.36 mg/kg (methamphetamine trained rats), ED_{50} = 0.52 mg/kg (cocaine trained rats).	--	Gatch *et al.*[30]
Drug discrimination: [c] 4-MEC (1.0-8.0 mg/kg) did not substitute for methamphetamine at any dose tested.	--	Naylor *et al.*[31]
Locomotor activity: [d] Small increases in forward locomotion and stereotypy at 3 mg/kg. Motor effects were short-lived and quickly returned to baseline values by 60 min after injection.	Microdialysis (rat nucleus accumbens): [d] Significant increase of extracellular 5-HT above baseline: 3.2-fold (1 mg/kg) and 6.9-fold (3.0 mg/kg). No effect on DA at 1 mg/kg but 1.9-fold increase of DA levels at 3 mg/kg.	Saha *et al.*[22]
Intracranial self-stimulation (ICSS): [e] Maximal reductions in ICSS thresholds observed with 4-MEC at 30 mg/kg (~15%) and were comparable with those observed with methamphetamine and α- PVP tested at the 0.3-	--	Watterson *et al.*[32]

mg/kg dose (~14%). ED_{50} values: 4-MEC (6.41 mg/kg), α- PVP (0.35 mg/kg), methamphetamine (0.20 mg/kg), MDPV (0.35 mg/kg), methylone (1.00 mg/kg).		
Locomotor activity and sensitization: [f] 4-MEC (30 mg/kg) and methamphetamine (1 mg/kg) significantly increased locomotor activity. 4-MEC: 10 to 30 min, methamphetamine: 15 to 95 min. A 3 or 10 mg/kg dose did not stimulate locomotor activity. Significant increase in total distance travelled following administration of methamphetamine (1 mg/kg) over 7 consecutive days and at rechallenge on day 22 compared to day one. 4-MEC (3, 10, or 30 mg/kg) did not induce increase activity of consecutive days with the exception of the rechallenge at day 22 (30 mg/kg). At rechallenge on day 22: 4-MEC (30 mg/kg) group exhibited enhanced locomotor activity from 5 to 35 min compared to methamphetamine (1 mg/kg), ranging from 5 to 100 min. Neither development nor expression of locomotor sensitization was observed with 4-MEC at 10 mg/kg. Elevated plus maze test: [g] Repeated injections of 4-MEC (30 mg/kg) decreased total travel distance with reduced percentages of travel distance and time spent in the open arm. Repeated methamphetamine administrations (3 mg/kg) significantly increased exploration. After a 2-week withdrawal period from chronic 4-MEC or methamphetamine injections, all rats exhibited abnormally reduced anxiety based on increased percentages of travel distance and time spent in the open arm. Conditioned place preference: (CPP): [h] Significant CPP at 10 mg/kg 4-MEC on day 9 and on day 24 (context-associated reinstatement test). No difference observed compared to methamphetamine that displayed CPP on both days at 1 mg/kg.	--	Xu *et al*.[33]

[a] Male Swiss-Webster mice (8 weeks old). Separate groups of 8 mice were injected with either 0.9% saline or a test drug (4-MEC at 3, 10, 30 or 100 mg/kg). Horizontal activity was measured for 8 h within 10-min periods. Behavioral observations were recorded on each mouse during the test sessions at 30, 120, and 480 min following 100 mg/kg 4-MEC. Other drugs for comparison included methcathinone, pentedrone, pentylone, and 3-fluoromethcathinone (3-FMC).

[b] Male Sprague-Dawley rats (two-lever choice methodology) trained to discriminate methamphetamine (1 mg/kg) and cocaine (10 mg/kg) from saline. 4-MEC (i.p., 1-50 mg/kg) was administered 30 min prior to the start of the test session.

[c] Male Sprague-Dawley rats (70 days old) trained to discriminate methamphetamine (1 mg/kg) from saline. Three synthetic cathinones, (4-MEC; 1.0-8.0 mg/kg), 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP; 4.0-16.0 mg/kg), and alpha-pyrrolidinopentiophenone (alpha-PVP; 0.25-2.0 mg/kg) were tested for their ability to substitute for methamphetamine. Cocaine (1.0-8.0 mg/kg) was used as positive and pentobarbital (1.0-8.0 mg/kg) as negative control. 4-MEC was administered 15 min prior to the start of the test session.

[d] Male Sprague Dawley rats. Rats received two i.v. drug injections, 1 mg/kg at time 0 followed by 3 mg/kg at the 60 min mark.

[e] Intracranial self-stimulation thresholds determined following acute 4-MEC administration (0.1, 0.5, 1 and 2 mg/kg, i.p.); bipolar electrode implanted into the medial forebrain bundLe. Drugs were administered 20 minutes prior to placement into ICSS procedures. Doses: 4-MEC (1-100 mg/kg) compared to alpha-pyrrolidinopentiophenone (α-PVP) (0.1-5 mg/kg) and methamphetamine (0.1-3 mg/kg). A 100-mg/kg dose for 4-MEC and 5-mg/kg dose for α-PVP were also administered for a subset of rats. However, ICSS thresholds increased instead of leading to a decrease.

[f] Male Sprague Dawley rats were injected once daily either with saline, 4-MEC (3, 10, or 30 mg/kg), or methamphetamine (1 mg/kg) for 7 consecutive days. Two weeks after last injection, each rat received the same drug. Locomotor activity was assessed for 120 minutes.

[g] Rats tested the day before the first drug injection, then 35 min following the first and last injections (3, 10, or 30 mg/kg for 4-MEC; 3mg/kg for methamphetamine), followed by a test 2 weeks of withdrawal.

[h] Rats received 4-MEC (1, 3, or 10 mg/kg, i.p.) or methamphetamine (1 mg/kg, i.p.) on days 1, 3, 5, and 7. Saline was administered on days 2, 4, 6, and 8. On days 9 and 24 (2 weeks after withdrawal), rats were allowed to explore the entire apparatus freely for 15 min.

5. Toxicology

Two *in vitro* studies have been published that report the evaluation of cytotoxicity using rat hepatocytes and HepaRG cells (Table 2). Under the conditions used (e.g. applied doses and incubation of test drugs for 48 h and 24 h at 37 °C), toxic effects were observed related to cell viability, oxidative stress and apoptosis.

6. Adverse Reactions in Humans

Since the previous critical review report on 4-MEC,[1] a number of new cases associated with 4-MEC intoxications and deaths have been reported in the scientific literature which are summarized in Table 4. In the majority of cases, the appearance of other substances and alternative causes of deaths (in case of fatal intoxications), however, placed a challenge on the ability to establish a direct link between 4-MEC intake and adverse drug reactions.

Table 4. Case reports associated with the involvement of 4-MEC reported in the scientific literature.

Year	Cases	Patient, age	Context/clinically related comments (examples)	Ref
2012	1	U [a]	Fatal 4-MEC intoxication with blood levels of 1267 ng/mL; cited in ref [34].	Rojek *et al.*[35]
2013	3	30M, 27M, UM [a]	Case 1 (fatal): Road traffic accident. Blood: 152 ng/mL 4-MEC and 0.12 g/dL ethanol; urine: 122 ng/mL 4-MEC and 0.19 g/dL ethanol. Case 2 (fatal): Blood: 56 ng/mL 4-MEC, PMA (2347 ng/mL), PMMA (30 ng/mL), amphetamine (378 ng/mL), methamphetamine (48 ng/mL), tetrahydrocannabinol (THC, 1.3 ng/mL) and 11-nor-9-carboxy-THC metabolite (8.7 ng/mL); urine: PMA (50.1 µg/mL), PMMA (1.7 µg/mL), 4-MEC (14.3 µg/mL), amphetamine and THCCOOH (54.7 ng/mL). Analysis of stomach contents: detection of PMA, PMMA and 4-MEC. Case 3 (NF, [b] clinical): White powder found in possession containing 4-MEC (78% purity). Blood analysis: 46 ng/mL 4-MEC. 2 Fatal, 1 NF: [b] Deaths not caused by 4-MEC intoxication.	Gil *et al.*[34]
2013	1	30M	Clinical case (NF [b]): User reported consumption of 10 g 4-MEC and 5 g of a branded product (NRG3) over 3 days and developed sudden outburst of aggression and tachycardia. Urine: MDMA (20 ng/mL), MDPV (20 ng/mL), 4-MEC (200 ng/mL). Hair: 4-MEC (30 ng/mg), MDPV (1 ng/mg), MDMA + MDA (2 et 0,1 ng/mg), mephedrone (0,1 ng/mg), cocaine (1,7 ng/mg) and metabolites (BZE = 0,2 + EME = 0,02 ng/mg), tramadol (3,5 ng/mg), hydroxyzine (0.14 ng/mg), aripiprazole (11 ng/mg) and haloperidol (0.01 ng/mg). Plasma: paracetamol (7 µg/mL), tramadol (465 ng/mL).	Knapp *et al.*[36]
2013	1	NR [c]	One analytical confirmed case by retrospective analysis of information from poison information center (Jan 2007-Dec 2012). No details reported.	Le Roux *et al.*[37]
2014	1	36M	Male (in psychotherapy for drug addiction and suicide attempts) found dead and suspected to be injecting drug user. Several marks from needle and a rectal foreign body were observed. Blood: hydroxyzine detected at therapeutic concentration (160 ng/mL); peripheral blood: 4-MEC at 14,600 ng/mL. Case considered fatal 4-MEC intoxication.	Bottinelli *et al.*[38]
2014	28	NR [c]	Review of casework carried out between Jan 2010 and Dec 2012. 28/203 cases involved detection of 4-MEC. No clear link between blood concentration levels and outcome. Example for drug deaths (including polydrug use, median): 0.46, 2.50, 5.83, 17.3 ng/mL; examples for non-fatal blood concentrations: 0.09, 0.20; examples for alternative causes of death: 0.28, 5.03 ng/mL.	Elliott and Evans[39]
2014	7	NR [c]	Review of casework of samples submitted between January 2010 and August 2011. Seven out of 189 cases included the detection of 4-MEC. One case was reported to confirm 4-MEC as the only substance detected and the poison severity score (PSS) was classified as "minor" (PSS = 1) in this case.	Helander *et al.*[40]
2014	1	36M	Fatal: Detected blood levels: 1200 ng/mL 4-MEC and 230 ng/mL amphetamine.	Rojek *et al.*[41]
2014	1	39M	Clinical case (NF [b]): injection of claimed 0.25-0.50 g of 4-MEC followed by γ-butyrolactone (GBL) consumption; patient found unconscious. Five hours following injection patient showed transient apnea requiring oxygen and stimulation. Patient woke up 30 min and remained confused for 4 h; discharged 13 h later. Blood and urine levels (8 h after injection): 353 ng/mL and 100 mg/L for 4-MEC and 300 mg/L and 1000 mg/L for	Turcant *et al.*[17]

			γ-hydroxybutyric acid (GHB).	
2015	1	21M	Clinical case (NF [b]): Severe decrease platelet numbers (thrombocytopenia) reported and associated with smoking 4-MEC and JWH-018 for 6 months. Evidence and analytical confirmation related to the presence of these particular two substances were not available.	Mocanu *et al.*[42]
2015	1	NR [c]	A death case was mentioned following consumption of a herbal mixture called "ACME" (containing JWH-210) and the ''bath salt'' product "9/11" (containing 4-methylethcathinone)". No further details reported.	Moosmann *et al.*[43]
2016	2	22M, 54M	Case 1 (considered 4-MEC drug death): Believed to have insufflated an unknown quantity of an NPS along with consumption of alcohol and use of cannabis; collapsed, started to convulse, coughed up blood and died ~4.5 h later in hospital. Femoral blood: ethanol (0.03 g/dL), 4-MEC (170 ng/mL), paracetamol (5,000 ng/mL). Ethanol (0.027 g/dL), 4-MEC and paracetamol were detected in urine qualitatively. Case 2: Male found dead with plastic carrier bag taped over his head. Femoral blood: 4-MEC (1730 ng/mL), ethanol (0.229 g/dL), propranolol (36 ng/mL), venlafaxine (284 ng/mL) and its metabolite *O*-desmethylvenlafaxine (205 ng/mL), diazepam (<5 ng/mL) and its metabolite nordiazepam (33 ng/mL). 4-MEC, ethanol, venlafaxine and O-desmethylvenlafaxine were detected qualitatively in urine. Propranolol and venlafaxine have been prescribed. Postmortem findings were consistent with asphyxia due to respiratory obstruction and significant left ventricular hypertrophy and coronary atheroma were reported.	Smith *et al.*[44]

[a] U: Unknown; UM: male with unknown age.
[b] NF: Non-fatal.
[c] NR: Not reported.

7. Dependence Potential

A. Animal Studies

No information available.

B. Human Studies

An analysis of 23 individual user trip reports and 112 screenshots of general 4-MEC user discussion boards revealed that the urge to redose when using 4-MEC was considered weak and short-lived with low incidence of negative comedown symptomatology (compared to mephedrone) although users with a history of synthetic cathinone use and less potent experiences with 4-MEC reported higher and more frequent dosing.[11]

8. Abuse Potential

A. Animal Studies

Data summarized in Table 3 suggest that 4-MEC shows potential for abuse. A comparison with psychostimulants such as mephedrone, cocaine and amphetamine suggest its potency may be lower as far as drug discrimination, locomotor activity and intracranial self-stimulation (ICSS) studies are concerned. A recent

microdialysis study carried out in conscious rats revealed a robust increase of 5-HT levels in dialysate obtained from rat nucleus accumbens. At the doses tested, small increases in dopamine levels were detected,[22] which might suggest a lower abuse potential compared to non-selective releasing agents such as mephedrone.[18, 19] This would be consistent with the data presented on reductions of ICSS thresholds at significantly higher dosage levels (Table 3). From this perspective, 4-MEC might display a profile more comparable to MDMA and methylone rather than methamphetamine or α-PVP.[32]

B. Human Studies

Information from formal clinical studies is not available. 4-MEC shows a psychostimulant profile in self reported users.[11, 45]

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Not applicable.

10. Listing on the WHO Model List of Essential Medicines

4-MEC is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

4-MEC is not marketed as a medicine.

12. Industrial Use

4-MEC has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence

Household surveys that specifically probe for prevalence of 4-MEC do currently not appear to be available in the published literature. Synthetic cathinones analyzed in drug samples submitted to a Spanish low-threshold drug testing Service between 2010 and 2012 revealed that 237 were submitted or identified to contain synthetic cathinones. 4-MEC was detected in 9.28% of the cases (methylone: 24.9%, mephedrone: 24.5% and MDPV: 6.8%).[46] Misrepresentation and detection of 4-MEC was reported on two occasions where users believed to have acquired either MDMA or ketamine.[47] The Trans European Drug Information (TEDI) project, where five low-threshold European drug-testing services collaborate (Spain, Switzerland, Belgium, Austria, Portugal, and the Netherlands) reported on the evaluation and analysis of samples derived from the cocaine, "ecstasy", and amphetamine market. The study reported the results obtained from 45,859 drug samples collected between 2008 and 2013. 4-MEC was detected in samples derived from the "ecstasy" market (tablets and powders) in Austria (2011-2013), Spain (2013), Switzerland (2013) but not in the Netherlands.[48]

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

The Hungarian National Focal Point reported that 4-MEC and MDPV dominated cathinone-related seizures in 2011 and it was observed that reduced availability of heroin on the market coincided with increasing changes in patterns related to injecting drug use, which included the use of 4-MEC.[49] A survey amongst a group of injecting users of new psychoactive substances, the highest mean number of times where 4-MEC was injected per day was 11.5,[50] thus, higher than what might be expected from heroin use. The combination of changing patterns in injecting drug users to new psychoactive substances (especially psychostimulants), a propensity to increased frequency and needle sharing, and economic challenges on harm reduction services, indicates increased vigilance and monitoring of incidences related to viral and bacterial infection rates.[50-52] Use of 4-MEC is also associated with the purchase of "research chemicals" or equivalent products *via* the Internet and possibly "smart" shops. Instances of misuse, abuse and dependence would be limited to individual users rather than the general population.

15. Licit Production, Consumption and International Trade

4-MEC is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses are not known.

16. Illicit Manufacture and Traffic and Related Information

Reports have been received from the EMCDDA's European Early-Warning System on new psychoactive substances that 4-MEC was encountered in seizures or as a used substance in Spain, Luxembourg, Greece, Turkey, Lithuania, Belgium, Norway, Italy, Austria, Slovakia, Malta, Slovenia, Croatia, Germany, Hungary, Bulgaria, France, Czech Republic, Finland, Denmark, and United Kingdom.[53]

The Drug Enforcement Administration disclosed that 374 exhibits were reported for 4-MEC between January 2010 and November 2013 which was based on STRIDE (System to Retrieve Information from Drug Evidence) database queries.[54] The National Forensic Laboratory Information System (NFLIS), which is dedicated to collect drug cases submitted to State and local laboratories in the United States registered 1952 reports containing 4-MEC between January 2010 and December 2013. In 2010, three out of 628 reports of synthetic cathinones from 27 States were reported to NFLIS.[55] Between April 2010 and November 2013, a total number of 78 encounters (shipments) with 4-MEC were identified by U.S. Customs and Border Protection.[56] The NFLIS 2014 Midyear Report (revised 2016), 2014 Annual Report and 2015 Midyear Report did not mention 4-MEC.[57-59]

4-MEC was reported to be the most common substance found in pills sold as "ecstasy" in the region of Oceania (at least in the time frame up to 2013).[60] Responses obtained to the UNODC questionnaire on NPS (up to 2012) revealed that 4-MEC was ranked fourth with regards to numbers of reports (38) received. This was only superseded by mephedrone (68 reports), MDPV (61 reports), methylone (53 reports) whereas flephedrone was ranked fifth (35 reports).[61] 4-MEC was reported 150 times to the UNODC Early Warning Advisory on New Psychoactive Substances by 41 Countries since 2009 (data for 2015 not yet completed).

The highest number of reports was received in 2013 (Dr. Justice Tettey, UNODC, personal communication).[62]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

4-Methylethcathinone (4-MEC) is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

The EMCDDA received information from the National Focal Points that 4-MEC is controlled in Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, United Kingdom and Turkey. The Russian Federation confirmed that 4-MEC is a controlled substance.[53] 4-MEC is controlled in the USA,[54] Singapore and New Zealand.

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

Not applicable.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of 4-MEC

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 45 Member States (5 AFR, 2 EMR, 25 EUR, 6 PAH, 1 SEAR and 6 WPR) answered the questionnaire for 4-Methylethcathinone (4-MEC). Of these, 26 respondents (21 EUR, 2 PAH and 3 WPR) had information on this substance.

LEGITIMATE USE

There were 25 countries that reported no approved medical products containing 4-MEC for human or veterinarian indications. There was also no reported industrial use in 22 countries.

4-MEC is currently being used in medical or scientific research in one country for metabolism and abuse potential research. Importation is the origin/source of 4-MEC was reported when used for legitimate non-medical/non-scientific use.

4-MEC was not reported to be used for any cultural, religious or ceremonial purposes in 22 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 18 countries that reported 4-MEC as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (13 countries), sniffing (10 countries), injection (4 countries), inhalation (2 countries) and smoking (1 country). The main route of administration for 4-MEC was specified as oral (7 countries) followed by sniffing (2 countries), insufflation (1 country) and smoking (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (16 countries), followed by tablets (5 countries), liquid or solution for oral administration/use (1 country) and injectable formulations (1 country). One country also reported plant material impregnated with the 4-MEC being used as a formulation.

There were 13 countries which reported that the source of 4-MEC for non-medical/non-scientific use was smuggling.

Party settings, people attending parties or dance festivals, are specified as a subpopulation known to misuse 4-MEC by two countries. Another country specified that youths and young adults were a subpopulation known to misuse 4-MEC.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (2 countries), substantial (5 countries) or serious (5 countries). For the countries that indicated a substantial or serious level of negative health-impact, they

specified that it was due to the association of 4-MEC with adverse events (including intoxications, transmission of communicable diseases through injection drug use), and fatalities. It was also mentioned that the pharmacodynamics of 4-MEC relate to those of MDMA and amphetamine. It was also commented that 4-MEC is a potent cathinone.

Five countries reported that there had been emergency room/department visits related to the non-medical use of 4-MEC. A combined number of 1 case in 2010, 1 case in 2011 and 4 cases in 2014 were reported. One country stated that it was implicated in one suicide and several hospitalisations in 2010/11. Two other countries specified that there had been a total of 2 emergency room/department visits but the details (including year) were not known.

The adverse effects which presented for 4-MEC at the emergency room/department included tachycardia, motor disorder, high respiratory rate, sweating, vertigo, anxiety, visual hallucinations and delirium.

In regards to the mortality rate, data was provided by 5 countries. The rate where only 4-MEC was involved included 1 case in 2011. The rate which included involvement of other substances was reported to be 2 cases in 2013 and 2 cases in 2016. Finally the rate, where it was unknown if other substances were involved was 1 case in 2011. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 24 countries reported that 4-MEC was under national control. The legislation the control is based upon included the Medicines Act (3 countries), Controlled Substances Act (18 countries), Criminal Law Act (2 countries) and other specific legislation (3 countries stated it was specific legislation for new psychoactive substances). In two countries the control is a temporary provision. One country reported that the use of Analog Act was a challenge to implementing controls for 4-MEC, as analog status had to be determined for each case.

The scope of the controls includes production (20 countries), manufacturing (22 countries), exporting (21 countries), importing (24 countries), distribution (23 countries), use (16 countries) and possession (22 countries).

Reported illicit activities involving 4-MEC include manufacture of the substance by chemical synthesis (2 countries), production of consumer products (1 country), trafficking (16 countries), smuggling (1 country), diversion (2 countries), domestic internet sales (2 countries), internet sales from abroad (9 countries), internet sales from unknown locations (6 countries) and finally sales to people who use this substance (5 countries).

There were 18 countries which completed the section on the number of seizures. The combined number of seizures was 362 (2014), 126 (2015) and 39 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If 4-MEC was placed under international control, 24 countries responded that they would have the capacity to enforce the control at the national level. There were 24 countries which responded that they would have the forensic laboratory capacity to analyse the substance.

Annex 2: Representative examples of studies associated with the detection and chemical analysis of 4-MEC (amongst other substances) published in the scientific literature since the 36th meeting of the WHO Expert Committee on Drug Dependence in June 2014.

Table 1. [a,1]

Techniques [b]	Comment	Reference
SRI-ToF-MS	Compounds obtained from test purchases.	Acton *et al.*[2]
LC-ESI-MS/MS	Development of screening method using dried blood spots (DBS).	Ambach *et al.*[3]
LC-ESI-Orbitrap-MS	Analysis of anonymised pooled urine from portable street urinals (City of Westminster, London, UK). Detection of 4-MEC in three urinals in July 2012.	Archer *et al.*[4]
IMS	Analysis of 4-MEC standard reference material.	Armenta *et al.*[5]
Immunoassays, LC-MS/MS	Evaluation of cross-reactivity in CEDIA, EMIT, and KIMS immunochemical screening assays for drugs of abuse; analysis of authentic urine samples.	Beck *et al.*[6]
GC-MS(/MS), LC-DAD	Quantification in blood obtained from a fatal intoxication case.	Bottinelli [7]
Immunoassay, LC-Q-Orbitrap-MS	Evaluation of the Randox Drugs of Abuse V (DOA-V) Biochip Array Technology; screening of 20,017 authentic military urine specimens.	Ellefsen *et al.*[8]
LC-DAD, LC-MS/MS, LC-QTOF-MS	Detection of 4-MEC in 28 forensic toxicology cases out of 203 cases between 2010 and 2012.	Elliott and Evans[9]
LC-MS/MS	4-MEC identified in 7 out of 189 cases (January 2010 to August 2011) submitted for toxicological analysis from emergency departments or intensive care units in Sweden.	Helander *et al.*[10]
Color test	Evaluation of reaction between 4-MEC and 2,4-dinitrophenylhydrazine (Brady's reagent).	Isaacs *et al.*[11]
GC-MS, LC-DAD, GC-FID, Orbitrap MS/MS	Analysis of branded products obtained from a local "head shop" in 2011.	Leffler *et al.*[12]
ME-FL, derivatization	Analysis of seized tablets.	Lloyd *et al.*[13]
ATR-FTIR, GC-MS	Analysis of street mephedrone (4-methylmethcathinone) samples. 4-MEC was detected in 10% of samples as an adulterant; 199 samples seized in South Wales (UK) between November 2011 and March 2013.	Miserez *et al.*[14]
LC-QTOF-MS	Development of screening method in spiked urine samples.	Paul *et al.*[15]
LC-MS/MS	Analysis of meconium and maternal hair.	Pichini *et al.*[16]
LC-MS/MS	Analysis of biological samples obtained from two fatal intoxications.	Rojek *et al.*[17]
Electroanalytical sensing	Voltammetric characterization of synthesized standards.	Smith *et al.*[18]

Electroanalytical sensing, LC-UV, LC-Orbitrap-MS	Voltammetric characterization of synthesized standards and application to four branded products (January 2013).	Smith *et al.*[19]
IMS-TOF-MS	Characterization of collected standards.	Sysoev *et al.*[20]
LC-DAD, LC-MS/MS, LC-QTOF-MS	Stability study in blood and plasma and detection in forensic casework samples.	Elliott and Soh *et al.*[21]
LC-MS/MS	Detection in fatal intoxication. [c]	Rojek *et al.*[17]
GC-MS, LC-Orbitrap-MS, NMR	Analysis of seized samples.	Strano Rossi *et al.*[22]
LC-MS/MS	Development of screening method in spiked human hair samples and application to authentic hair samples.	Strano-Rossi *et al.*[23]
CE and MEKC-DAD and MS/MS	Analysis of standard reference material.	Švidrnoch *et al.*[24]
Immunoassay	Sixteen immunoassay kits were obtained from four commercial manufacturers to evaluate cross-reactivities in human serum.	Swortwood *et al.*[25]
LC-DAD, GC-MS, LC-MS/MS, LC-Q-Orbitrap-MS	Detection of 4-MEC and GHB (GBL consumption) in blood and urine in an intoxication case.	Turcant *et al.*[26]
Portable NIR, GC-MS	Analysis of standard reference material and forensic samples.	Tsujikawa *et al.*[27]
GC-MS	Screening of 34,561 authentic urine samples collected between February 2011-January 2013 (4-MEC positive: 0.19%).	Uralets *et al.*[28]
GC-MS, FTIR, NMR, WD-XRF, UV-Vis	Analysis of 13 branded products purchased in different ‘‘smart shops’’ in the area of Lisbon, Portugal.	Zancajo *et al.*[29]
LC-MS/MS	Development of screening method in spiked blood and human urine samples.	Ambach *et al.*[30]
GC-MS, NMR, elemental analysis	Analysis of 27 branded products purchased in three different Portuguese “smartshops” during 2012 and 2013 and evaluation of hepatotoxic effects *in vitro*.	Araújo *et al.*[31]
GC-MS, TOF-MS, LC-DAD, ATR-FTIR, IMS	Analysis of 38 purified new psychoactive substances (NPS).	Armenta *et al.*[32]
LC-TOF-MS	Mixed-mode chromatography study using standard reference material.	Clyde *et al.*[33]
LC-Q-Orbitrap-MS	Development of screening method in human urine and application to authentic urine specimen (4-MEC detected in 3/49 samples).	Concheiro *et al.*[34]
IMS, DART-QTOF-MS	Analysis of standard reference material.	Gwak and Almirall *et al.*[35]
GC-(EI/CI)-MS/MS	Analysis of standard reference material.	Gwak *et al.*[36]
GC-MS, LC-Q-Orbitrap-MS	Phase I and phase II metabolism study in human urine and incubation in pooled human liver microsomes.	Helfer *et al.*[37]
CE-ESI-MS	Analysis of standard reference material.	Moini *et al.*[38]
DLLME, LC-MS/MS	Development of screening method in spiked blood and application to authentic forensic blood samples (4-MEC detected in 1/60).	Odoardi *et al.*[39]

SFC, LC-DAD, LC-MS/MS	Analysis of standard reference material.	Pauk *et al*.[40]
LC-MS/MS	Development of screening method for analysis of wastewater and river water and application to authentic water samples in Croatia; 4-MEC not detected.	Senta *et al*.[41]
LC-AD	Method development and application to five branded products (January 2013).	Zuway *et al*.[42]
ELISA, LC-DAD, LC-MS/MS	Detection of 4-MEC in 3/112 forensic blood samples (review).	Adamowicz *et al*.[43]
LC-MS/MS	Method development and application to authentic samples. Detection of 4-MEC in 3/112 forensic blood samples.	Adamowicz and Tokarczyk[44]
CEC-DAD, SFC-DAD, LC-DAD	Chiral analysis of purchased samples or police samples.	Albals *et al*.[45]
LC-QTOF-MS	Development of screening method for analysis of sewage samples and pooled urinals from music festivals in Norway (4-MEC not detected).	Baz-Lomba *et al*.[46]
Color spot tests, LC-DAD, GC-MS, TLC, UV-Vis	Analysis and detection of NPS in samples from the ecstasy market (tablets and powders) in five European drug-testing services between 2008-2013.	Brunt *et al*.[47]
GC-MS, DART-Q-Orbitrap-MS/MS	Analysis of standard reference material and two tablets.	Chen *et al*.[48]
SFC-LC-DAD	Chiral analysis of collected samples.	Geryk *et al*.[49]
LC-MS/MS	Analysis of urban wastewater sampled in several cities in four European countries. 4-MEC was detected in samples obtained from two cities (Italy and UK).	Gonzalez-Marino *et al*.[50]
GC-MS	Thermal degradation study using standard reference material.	Kerrigan *et al*.[51]
SERS, GC-MS, IR	Analysis of seized tablets and standards.	Lee *et al*.[52]
VAMS, LC-MS/MS	Development of screening method for analysis of urine, plasma and oral fluid and application to samples from self-reported users.	Mercolini *et al*.[53]
GC-MS, LC-Orbitrap-MS	4-MEC detected in 33/162 samples obtained from Internet purchases and seizures between 2013 and 2015.	Odoardi *et al*.[54]
LC-MS/MS	Development of screening method in spiked human hair samples and application to authentic hair samples (4-MEC detected in one sample).	Salomone *et al*.[55]
qNMR	Evaluation of signal integration functionalities.	Schoenberger *et al*.[56]
LC-UV	Chiral separation of branded products obtained from "smart shops"[31]	*Silva et al*.[57]
LC-MS/MS	Two fatal intoxications and detection in femoral blood and urine.	Smith *et al*.[58]
LC-TOF-MS	Analysis of urine samples from volunteers at two healthcare centers (4-MEC detected in 1/101 samples).	Sundström *et al*.[59]
LC-MS/MS	Development of screening method for analysis of blood samples and application to authentic forensic blood	Vaiano *et al* [60]

	samples (4-MEC not involved).	
LC-DAD, NMR,	Chiral analysis of standards and donated samples.	Wolrab *et al*.[61]

[a] As of August 2016.

[b] SRI: selective reagent ionization; TOF: time-of-flight; MS: mass spectrometry; LC: liquid chromatography (various forms); ESI: electrospray ionization; MS/MS: tandem mass spectrometry; IMS: ion mobility spectrometry; Q: quadrupole; DAD: diode array detection; QTOF: quadrupole-time-of-flight; GC: gas chromatography; FID: flame ionization detection; ME: microchip electrophoresis; FL: fluorescence detection; ATR-FTIR: attenuated total reflection Fourier transform infrared; NMR: nuclear magnetic resonance spectroscopy; CE: capillary electrophoresis; MEKC: micellar electrokinetic chromatography; GHB: γ-hydroxybutyric acid; GBL: γ-butyrolactone; NIR: near infrared spectroscopy; WD-XRF: wavelength dispersive X-ray fluorescence; UV-Vis: ultraviolet-visible light spectroscopy; DART: direct analysis in real time; EI: electron ionization; CI: chemical ionization; DLLME: dispersive liquid/liquid microextraction; SFC: supercritical fluid chromatography; AD: amperometric detection; ELISA: enzyme-linked immunosorbent assay; CEC: capillary electrochromatography; SERS: surface-enhanced Raman spectroscopy; VAMS: volumetric absorptive microsampling; qNMR: quantitative NMR;

[c] Article cited in previous Critical Review report[1] as "in press".

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